[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF NEW HAMPSHIRE]

Rearrangement of the Triphenylmethyl Ethers of Ortho Cresol and Brominated Ortho Cresols

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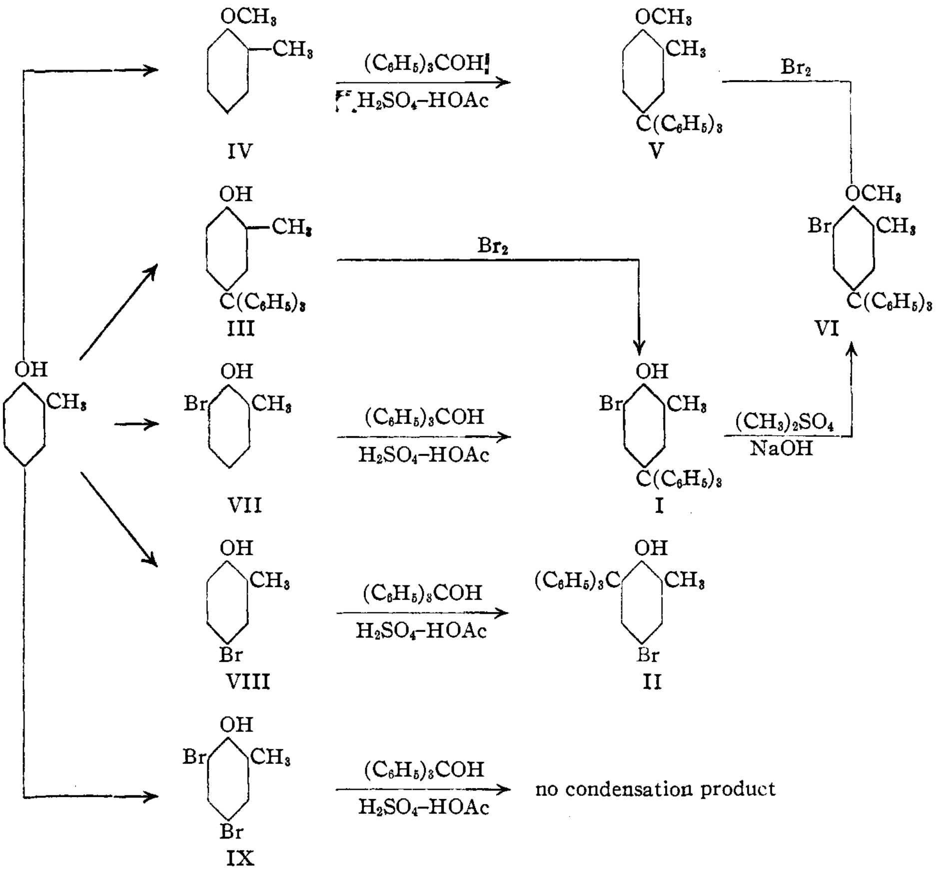
In a previous communication[1] a derivative of the postulated rearrangement product[2,3] from the triphenylmethyl ether of *o*-cresol was reported. However, the synthetic α-2-methoxyphenyl-β,β,-β-triphenylethane possessed a lower m. p. of 142–143° than the methylated cryptophenol, m. p. 165°, which supported the interpretation[4] that the triphenylmethyl group had not migrated to the side chain of *o*-cresol.



To substantiate the alternate hypothesis that migration involves a ring position, certain positions in the *o*-cresol molecule were blocked by bromine atoms, thus limiting the possible positions which a triphenylmethyl group might enter in the ensuing ether rearrangement or direct condensation reactions. The products of these reactions were then compared with the brominated product from the cryptophenol under consideration. This is shown in the accompanying schematic set of reactions.

Parallel condensations were made using triphenylcarbinol, sulfuric acid and glacial acetic acid on 6-bromo-*o*-cresol, VII, 4-bromo-*o*-cresol, VIII, and 4,6-dibromo-*o*-cresol, IX. In the case of VII, in which a para position is free, a good yield (55%) of product I was obtained, whereas using VIII in which an ortho position is open, there was a low yield of product (6.75%) and no condensation product from IX could be recovered. Further by adding an equivalent of bromine to the cryptophenol III[2] in carbon tetrachloride solution, the same monobrominated product I was obtained, which indicates the entrance

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(1) Iddles, French and Mellon, THIS JOURNAL, **61**, 3192 (1939).
(2) Schorigin, *Ber.*, **59**, 2502 (1926).
(3) Van Alphen, *Rec. trav. chim.*, **46**, 287 (1927).
(4) Boyd and Hardy, *J. Chem. Soc.*, 630 (1928).

of bromine into position 6 and indirectly that position 4 must be occupied by the triphenylmethyl group prior to bromination.

Since Boyd and Hardy[4] had condensed *o*-methoxytoluene with triphenylcarbinol in an acid medium and then brominated the resulting methyl ether to give a product, m. p. 180°, to which they assign structure VI, the present structure I was methylated and found to produce a material with the same m. p., 183–184°. Thus it is shown in preparing product I by two routes and product VI by two different sets of investigators and procedures, a common product was formed in each case.

In reactions[2,5,6,7] leading to the formation of the triphenylmethyl ethers of the three brominated *o*-cresols, an ether was produced from VIII but no ether formation occurred with VII and IX, apparently due to spacial hindrance. However, from VII a good yield of rearranged product I, m. p. 152°, was produced directly, agreeing with the compound prepared by the two procedures described above.

Experimental

Preparation of Brominated Cresols.—The 6-bromo-*o*-cresol VII was prepared by the procedure of Huston and Neeley.[8] The 4-bromo-*o*-cresol VIII was prepared as described by Goldschmidt, Schulz and Bernard.[9] The 4,6-dibromo-*o*-cresol IX was prepared similarly by dissolving 27 g. of *o*-cresol in 90 ml. of carbon tetrachloride and adding 80 g. of bromine in 10 ml. of carbon tetrachloride to the cooled, stirred solution during a two-hour period. After standing for fifteen minutes, yellow needles separated. These were filtered off and the mother liquor evaporated under reduced pressure to yield several further crops. Recrystallization from alcohol yielded a colorless product, m. p. 56.5–57.5°, in a 70% yield.

Condensation of *o*-Cresol and Triphenylcarbinol.—The rearranged product resulted as described previously.[1]

Condensation of 6-Bromo-*o*-cresol VII and Triphenylcarbinol.—Twenty grams of 6-bromo-*o*-cresol, 135 g. of glacial acetic acid, and 4.5 g. of triphenyl-carbinol were mixed and 23 g. of sulfuric acid was added dropwise, producing a deep reddish-brown coloration. After standing for three weeks, the solution was poured into 1500 ml. of water, producing a deep violet solution and a slight precipitate. The solution and solid were extracted with ether, washed with 10% sodium hydroxide to remove unreacted 6-bromo-*o*-cresol, then with water and dried over anhydrous sodium sulfate. After distilling off the ether the remaining amber oil was dissolved in 500 ml. of ligroin and extracted with Claisen's solution. The extract was acidified with hydrochloric acid, producing a precipitate which was recrystallized from alcohol or ligroin giving a 55% yield, m. p. 149–151°.

Anal. Calcd. for $C_{26}H_{21}OBr$: Br, 18.61. Found: Br, 18.39, 18.29.

Condensation of 4-Bromo-*o*-cresol VIII and Triphenylcarbinol.—4-Bromo-*o*-cresol, 26 g., was mixed with 135 g. of glacial acetic acid and 4.5 g. of triphenylcarbinol and 23 g. of sulfuric acid added slowly. No solid separated after standing for several weeks. Then the solution was poured into two liters of water, producing a black oil which was extracted with ether. After washing the ether extract with 10% sodium hydroxide, 21 g. of unchanged 4-bromo-*o*-cresol was recovered by acidifying the basic washings. The ether layer was dried and evaporated to yield a brown oil which was taken up in ligroin. Treatment with Claisen's solution, followed by acidification, gave a product which was recrystallized from alcohol with a yield of 0.5 g. or 6.75%, m. p. 208–209°.

Anal. Calcd. for $C_{26}H_{21}OBr$: Br, 18.61. Found: Br, 18.81, 18.57.

Attempted Condensation of 4,6-Dibromo-*o*-cresol IX and Triphenylcarbinol.—When the dibromo-*o*-cresol was carried through the usual condensation procedure, no significant condensation product could be recovered in the various steps of recovery.

Bromination of Schorigin's Cryptophenol III.—The simple cryptophenol (m. p. 180–183°), 7 g., was dissolved in 325 ml. of carbon tetrachloride, a few tacks were added and, while cooling and stirring, one equivalent (3.2 g.) of bromine dissolved in 25 ml. of carbon tetrachloride was added slowly. As the reaction proceeded the remaining cryptophenol dissolved and hydrogen bromide was evolved. After standing six hours, the reaction mixture was washed with water, dried with anhydrous sodium sulfate and then evaporated under reduced pressure. A creamy residue resulted which was recrystallized from ligroin (70–90°) and gave 7.35 g. or 85.7% yield, m. p. 149–151°. A mixed melting point with I obtained by the condensation of 6-bromo-*o*-cresol and triphenylcarbinol, also m. p. 149–151°, gave no depression and thus they were proved to be identical.

Methylation of Compound I.—One gram of the monobrominated cryptophenol I, dissolved in 50 ml. of benzene, was refluxed with 30 g. of sodium hydroxide in 60 ml. of water while adding 2 g. of dimethyl sulfate during a period of fifteen minutes. After one-half hour, another portion of alkali was added to destroy excess of dimethyl sulfate. Following ether extraction, washing with water and drying, the solvents were partially evaporated. Upon addition of ligroin (70–90°) crystallization resulted yielding 0.8 g. of product, m. p. 183–184°. By another synthesis[4] this product was found to melt at 180°.

Preparation of Rearranged Compound from 6-Bromo-*o*-cresol VII and Triphenylchloromethane.—In an attempt to prepare the triphenylmethyl ether of 6-bromo-*o*-cresol, 19 g. of the cresol was dissolved in 50 ml. of dry ether and 2.3 g. of sodium added. After complete reaction of the sodium, 15 g. of triphenylchloromethane dissolved in 200 ml. of dry ether was added and the reaction mixture refluxed for five hours. The cooled ether layer was washed with water and carried through the usual treatments with

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(5) Gomberg and Kamm, This Journal, **39**, 2013 (1917).

(6) Baeyer and Villiger, *Ber.*, **35**, 3018 (1902).

(7) Claisen, *Ann.*, **418**, 69 (1919).

(8) Huston and Neeley, This Journal, **57**, 2176 (1935).

(9) Goldschmidt, Schulz and Bernard, *Ann.*, **478**, 14 (1930).

10% sodium hydroxide and Claisen's extraction of a ligroin solution. Upon acidification of the two alkaline solutions, 9.5 g. (41.5%) of product, m. p. 150–152°, was obtained. This agreed by mixed melting point and analysis with the rearranged product I obtained by the direct condensation above. Further attempts to prepare the ether using potassium, potassium carbonate and acetone or a pyridine medium produced varying quantities of the same rearrangement product.

Attempted Preparation of Triphenylmethyl Ether of 4,6-Dibromo-*o*-cresol IX.—Ten grams of the 4,6-dibromo-*o*-cresol was treated with 1.5 g. of sodium in dry ether and 10 g. of triphenylchloromethane was added. After refluxing and carrying out the usual steps of recovery, no ether could be obtained but a large portion of the original brominated *o*-cresol and triphenylcarbinol was recovered.

Preparation of the Triphenylmethyl Ether of 4-Bromo-*o*-cresol VIII.—Eleven grams of 4-bromo-*o*-cresol was dissolved in 45 ml. of pyridine (dried and distilled from barium oxide) and 15 g. of triphenylchloromethane was added. After heating the mixture for ten hours, water and ether were added and the ether layer was washed with dilute hydrochloric acid, then with 10% sodium hydroxide and finally with water. After drying the ether layer and evaporation, the residue was taken up in ligroin (70–90°) and washed with Claisen's solution. No product was removed by the alkaline washing but from the ligroin layer, a product was obtained which was recrystallized from alcohol. A yield of 11.25 g. or 48.7%, m. p. 113.5–114°, was obtained.

Anal. Calcd. for $C_{26}H_{21}OBr$: Br, 18.61. Found: Br, 18.74, 18.65.

Attempted rearrangement of this ether in glacial acetic acid-sulfuric acid mixtures by dry hydrogen chloride or by zinc chloride was unsuccessful. Only small portions of triphenylcarbinol could be recovered in each case.

Conclusions

Condensation products have been obtained from the reaction in acid medium of triphenylcarbinol on 4-bromo-*o*-cresol VIII and 6-bromo-*o*-cresol VII. The latter product I agreed with the substance obtained by mono-bromination of Schorigin's cryptophenol. Methylation of product I gave a substance agreeing with the material prepared in a different series of steps by Boyd and Hardy[4] and postulated to have structure VI. Thus from these two reaction cycles the evidence places the triphenylmethyl group in the para position in the simple cryptophenol, as shown in structure III.

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Sterols. LXXXII. Estrane Derivatives

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Although the catalytic hydrogenation of estrone has been studied by a number of investigators,[1–5] the only reduction products which have been studied to any extent are the isomeric estradiols and an estranediol-3,17(α). This latter product is of considerable interest inasmuch as it is undoubtedly identical with one of the estranediols isolated from human non-pregnancy urine.[6,7] No information has been presented concerning the configurations at C-5 and at C-3 of this substance. The problem concerning the isomeric reduction products of estrone is complicated by the fact that the C-10 position becomes an asymmetric center during the course of the reduction. Thus the reduction of α-estradiol theoretically could give rise to eight isomeric estranediols. The fact that an isomeric estranediol, m. p. 242°, was isolated from human non-pregnancy urine[6,7] indicates that additional isomers exist. This particular estranediol-3,17 has not as yet been encountered in the *in vitro* reduction of estrone.

The fact that the catalytic hydrogenation of estrone in acidic medium results in the formation of mono-hydroxyestranes is of interest and in this respect it would appear to be analogous to equilenin, which readily yields a monohydroxy compound on reduction under similar conditions.[8,9,10] Dirscherl[4] has reported the isolation of two estranols from the reduction products of estrone in acidic ethanol. Butenandt[1] reported that in the hydrogenation of estrone acetate in neutral ethanol with platinum oxide catalyst the carbonyl group is reduced to a methylene group, the aromatic ring reduced and the acetate residue re-

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(1) Butenandt, *Z. physiol. Chem.*, **191**, 140 (1930).

(2) Butenandt, Stormer and Westphal, *ibid.*, **208**, 149 (1932).

(3) Butenandt and Westphal, *ibid.*, **223**, 147 (1934).

(4) Dirscherl, *ibid.*, **239**, 53 (1936).

(5) Marker and Rohrmann, THIS JOURNAL, **60**, 2927 (1938).

(6) Marker, Rohrmann, Wittle and Lawson, *ibid.*, **60**, 1512 (1938).

(7) Marker, Rohrmann, Lawson and Wittle, *ibid.*, **60**, 1901 (1938).

(8) Marker, Kamm, Oakwood and Tendick, *ibid.*, **59**, 768 (1937).

(9) Ruzicka, Muller and Morgeli, *Helv. Chim. Acta*, **21**, 1394 (1938).

(10) Marker and Rohrmann, THIS JOURNAL, **61**, 3314 (1939).